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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/803,702	02/21/1997	VERNON C. MAINO	P-3639P1	9092

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 06/13/2003

44

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
08/803,702	Maino et al.
Examiner	**Art Unit**
G.R. Ewoldt, Ph.D.	1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) [X] Responsive to communication(s) filed on *Mar 31, 2003* .

2a) [X] This action is **FINAL**. 2b) [ ] This action is non-final.

3) [ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) [X] Claim(s) *19-24, 26-55, and 61-63* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) [ ] Claim(s) _____ is/are allowed.

6) [X] Claim(s) *19-24, 26-55, and 61-63* is/are rejected.

7) [ ] Claim(s) _____ is/are objected to.

8) [ ] Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) [ ] The specification is objected to by the Examiner.

10) [ ] The drawing(s) filed on _____ is/are a) [ ] accepted or b) [ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) [ ] The proposed drawing correction filed on _____ is: a) [ ] approved b) [ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) [ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) [ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) [ ] All b) [ ] Some* c) [ ] None of:

1. [ ] Certified copies of the priority documents have been received.
2. [ ] Certified copies of the priority documents have been received in Application No. _____ .
3. [ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) [ ] The translation of the foreign language provisional application has been received.

15) [ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [ ] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) [ ] Interview Summary (PTO-413) Paper No(s). _____
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [ ] Other:

DETAILED ACTION

1. Applicant's amendment, remarks, and drawings, filed 3/31/03, are acknowledged.

2. Applicant's new drawings have been found acceptable by the Examiner.

3. Claims 19-24, 26-55, and 61-63 are under examination.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 19-24, 26-55, and 61-63 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the reasons set forth in Papers No. 24, 28, 33 and 40, mailed 1/30/01, 8/31/01, 2/26/02, and 12/02/02 respectively.

Applicant's arguments, filed 3/31/03, have been fully considered but they are not persuasive. Applicant argues, "Applicants maintain that the rejection is improper and contradicts the precedent of the case law cited herein. The description need only describe in detail that which is new or not conventional, and this aspect of the claimed method is old in the art. In particular, where claims are drawn to the use of known compounds, as they are in the present case, and are not drawn to either novel compounds per se or methods using novel compounds, the applicant is not required to discover all the compounds from this class that would be useable in the methods."

First note that Applicant's assertions comprise only attorney's argument; said argument cannot be considered evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art. Additionally, the arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common

experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration MPEP 2145. Accordingly, Applicant's assertion that the term "an inhibitor of cytokine secretion" is well-known in the art is insufficient to overcome the rejection. Applicant's additional citation of case law is then irrelevant because the assertion upon which the argument is based, and which the case law is presented to support, has not been established to be fact.

Also note, however, that Applicant appears to be arguing that certain parts/aspects of the invention are new while other parts are not. In fact, none of the individual pieces of the claimed method are actually new, i.e., the activation of antigen-specific T cells is not new and neither is the detection of intracellular cytokines. What is new is the *combination* of techniques and steps that achieve an unexpected result, i.e., the detection of cytokines that were thought to exist at levels below the threshold of detectability. Accordingly, each aspect of the new and unexpected method must be adequately described for the claims to meet the written description requirement.

Further note that Applicant has failed to address the Examiner's points regarding whether or not chemicals such as azide, chloroquine, cytochalasin, bafilomycin, or vincristine would be considered to be inhibitors of cytokine secretion in the claimed method. This line of reasoning can be carried a step farther - would the claims encompass the use of an anti-sense nucleic acid that could inhibit cytokine secretion (by blocking the expression of proteins involved in secretion)? Most certainly there exist chemicals or compounds that are not well-known in the art as inhibitors of cytokine secretion that could inhibit said secretion. As set forth previously essentially any toxin, e.g., bleach or benzene, would meet the limitation, yet not be considered an inhibitor of cytokine secretion. Previously Applicant argued that only BFA and monensin should be considered as such. Now Applicant appears to have replaced that argument in favor of an argument that essentially says, "if a compound/composition works in the method, it is encompassed by the method". This line of reasoning seems to be inconsistent with Applicant's previous position.

6. Claims 19-24, 26-55, and 61-63 stand rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Elements critical or essential to the practice of

the invention, but not included in the claims are not enabled by the disclosure, for the reasons of record set forth in Paper No. 40, mailed 12/02/02.

Applicant's arguments, filed 3/31/03, have been fully considered but they are not persuasive. Applicant argues, "Applicants respectfully point out that the premise on which the rejection is based is not valid, as the unexpectedness of the claimed invention is based on the understanding and expectation of one [of] skill in the art at the time of the invention, without benefit of Applicants' teaching, rather than on the enablement provided in the specification."

It is the Examiner's position that the method recited in the claims would produce highly unpredictable results because it is not the method disclosed in the specification, i.e., the claimed method lacks many steps (as set forth in the rejection) that are necessary to achieve the unexpected results.

Applicant argues that even the declaration of Dr. Altman provides expert testimony that the Applicant's achieved unexpected success with the method of the specification.

It is the Examiner's position that the method recited in the claims is not the method of the specification because it lacks many of the required steps set forth in the specification. As set forth in the previous action, the specification itself discloses the terms "critical" and "required" (see, for example, Claim 4).

Applicant continues "Applicants wish to point out that the facts in the present case are distinguished from those in *In re Mayhew*, cited by Examiner as precedence for the rejection. In *In re Mayhew*, the specification contained multiple teachings that the invention was dependent on a specific feature (a cooling zone, specifically located), and this feature was omitted entirely in the broadest claim."

It is the Examiner's position that this appears to be a highly analogous to the situation in the instant application, i.e., specific features on which the claimed method depends are absent from the claims.

Regarding Applicant's amending of "contacting" to "culturing" the amendment is noted. Accordingly, one critical factor has been added to the claims, others, as set forth previously, still remain absent.

Applicant argues "The examples illustrate certain preferred embodiments of the invention but are not intended to be illustrative of all embodiments (specification, page 13, lines 16-17). In particular, Example 4 provides teaching of a preferred embodiment which maximizes response and accuracy of detection, including the use of slant tubes to maximize response, gating using CD69, the timing of the introduction of Brefeldin A to maximize response, and number of events collected to achieve detection accuracy."

Again, it is noted that Example 4 in particular discloses that certain steps or reagents are "critical" and "required". These terms were chosen by Applicant for inclusion in the specification, not by the Examiner. Applicant may not now reasonably argue that that which is disclosed as essential is not really so.

Applicant argues "Examiner stated that the specification and the post-filing art disclose/teach that the inclusion of an inhibitor of cytokine secretion is essential (Paper 40, page 5). As discussed above with respect to written description, the use of an inhibitor of cytokine secretion to allow accumulation of cytokines within activated T cells was known in the art. One of skill in the art, following the teaching of the specification and without undue experimentation, could carry out the claimed methods using a known inhibitor of cytokine secretion.

It is noted that Applicant has *not* argued that an inhibitor of cytokine secretion is *not* essential. Accordingly, in this regard at least, Applicant appears to not traverse the rejection.

Applicant argues "Examiner cited O'Neil-Andersen and Lawrence ("O'Neil-Andersen") as teaching that different inhibitors of cytokine secretion, Brefeldin A (BFA) and monensin (MN), would yield different results. O'Neil-Andersen describes the use of BFA and MN as inhibitors of cytokine secretion in flow-cytometric assays for the detection of intracellular cytokines following general activation of T cells in a non-specific manner (using PMA and ION). The methods are equivalent to those described in the art of record."

It appears by Applicant's last statement that in Applicant's opinion, the method of the instant claims is neither novel nor unobvious because "The methods are equivalent to those described in the art of record." Applicant is advised that such a position would seem to require that the previous art rejection based on

obviousness be reinstated. It is the Examiner's position that the invention is indeed novel and unobvious because detection of intracellular cytokines was unexpectedly achieved in T cells that were antigen-specifically activated, i.e., only a small percentage of the T cells were activated (in contrast to the method of the references in which the majority of the T cells were non-specifically activated). Additionally, Applicant has not addressed the facts of the references, i.e., that the authors teach that "the choice of a protein transport inhibitor is an important variable". It would seem that the choice would be all the more important in a method in which only a small percentage of the cells are activated. Accordingly, the use of *any* inhibitor of cytokine transport is considered to be highly unpredictable.

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321c may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19-24, 26-55, and 61-63 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-37 and 39-40 of copending Application No. 09/526,253. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications recite claims drawn to a method of detecting antigen-specific lymphocytes comprising flow cytometrically detecting a cytokine and a T cell subset in the presence of a protein synthesis inhibitor. Note that at the time of the restriction of the '702 application the claims of said application were drawn to a method of detecting antigen-specific

cytokine production. Subsequent amendment of the claims of the '702 application has necessitated this rejection. Further note that the claims of the '702 application are drawn to "an MHC-dependent nominal antigen" while the claims of the '253 application are drawn to a "vaccine antigen". However, neither antigen is defined in the specifications and said antigens are not considered to be patentably distinct. Other dependent claims of both applications recite various combinations of costimulation antigens, cytokines, and accessory molecules such as chelators and fluorophores.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant indicates that the issue will be addressed upon the finding of allowable subject matter in the '253 application.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805 The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should

be faxed to Technology Center 1600 at 703-872-9306 (before final) and 703-872-9307 (after final).

G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600
June 12, 2003